Targeted *in vivo* generation of CAR T and NK cells utilizing an engineered lentiviral vector platform

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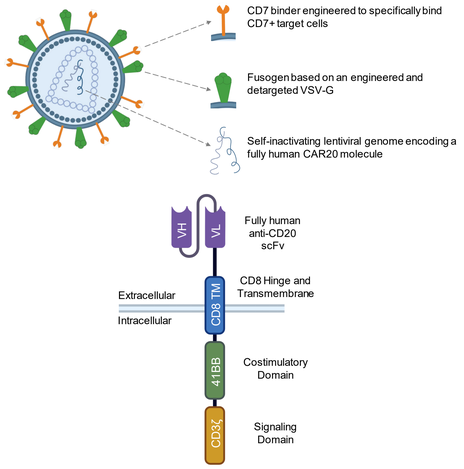
Proprietary platform for *in vivo* gene delivery

CAR T cell therapies have revolutionized treatment of B cell malignancies. *Ex vivo* CAR T cell manufacturing is complex, costly, and cumbersome, prompting efforts that support shorter manufacturing processes and allogeneic or "universal donor" strategies. Recent data show that CAR T product efficacy is correlated with reduced *ex vivo* manipulation of cells. We have designed a system to transduce target cells *inside the body* to generate autologous CAR cells, circumventing *ex vivo* manipulation, avoiding the need for conditioning chemotherapy, and providing an "off-the-shelf" therapy for B cell malignancies.

INT2104 is a non-replicating, self-inactivating lentiviral vector delivering a transgene for a CAR specific for CD20 (CAR20). The lentiviral vector is designed to generate CAR T and CAR NK cells *in vivo* following a single intravenous administration of the viral vector.

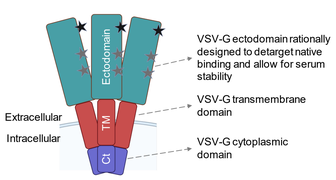
INT2104



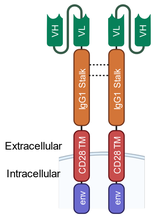
Rationally designed vector components

- Targeted delivery of INT2104 is enabled by engineered fusogen and binder components incorporated within the lentiviral vector
- Proprietary fusogen mutated to blind native binding of vesicular stomatitis virus G (VSV-G) to the LDL receptor while maintaining pH-dependent fusion
- CD7 Binder incorporates a proprietary human and NHP cross-reactive scFv with a human IgG1-based stalk to specifically target particles to CD7$^+$ cells

Fusogen

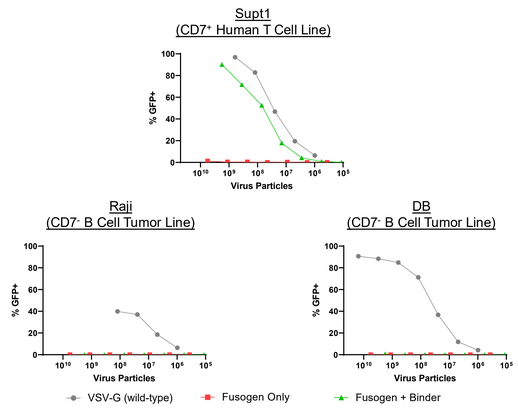


CD7 Binder



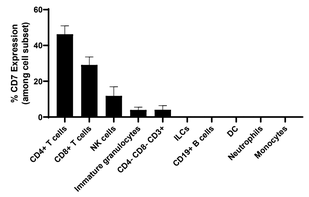
Specific transduction of CD7$^+$ cells

- *In vitro* screening of INT2104 with GFP-encoding vectors revealed dose-dependent transduction of CD7$^+$ target cells
- No transduction evident when adding INT2104 to CD7$^-$ B cell lines



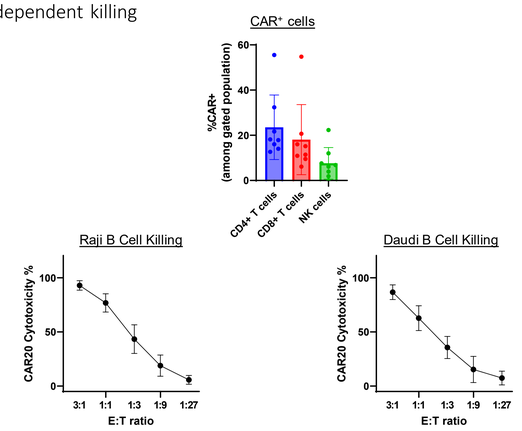
CD7 distribution in primary human PBMCs

- Screening of PBMCs from ten unique human donors reveals T cells (both CD4$^+$ and CD8$^+$) and NK cells are the majority of cells expressing CD7 in blood
- These cells are the potential targets of INT2104 and are intended to provide the therapeutic benefit



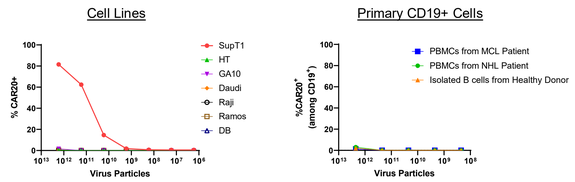
CAR mediated, dose-dependent B cell killing

- Incubation of activated primary human PBMCs with INT2104 generates CD4$^+$ T cells, CD8$^+$ T cells, and NK cells that are CAR$^+$
- CAR$^+$ cells co-cultured with B cell tumor targets show dose-dependent killing



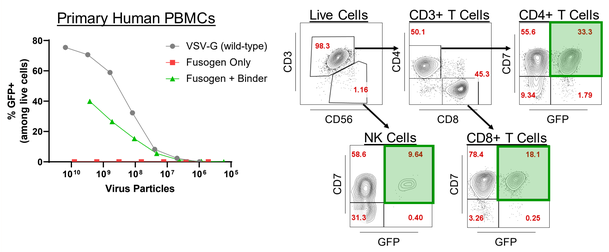
No B cell transduction detected following INT2104 treatment

- Further assessment into potential off-target transduction of B cells was conducted with six B cell tumor lines and primary PBMCs isolated from patients with B cell malignancies which were inoculated with INT2104
- No evidence of B cell transduction was seen across a wide range of MOIs



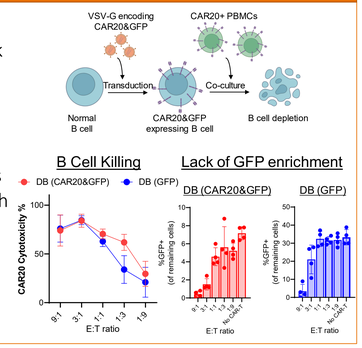
Transduction of both T cells and NK cells

- Inoculation of activated primary human PBMCs with GFP-encoding vectors results in transduction of intended cell targets



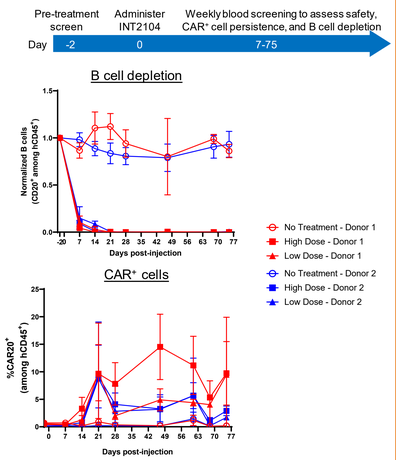
Killing of CAR$^+$ B cells with INT2104-treated cells

- An experiment was performed to assess the risk of unintended B cell transduction resulting in CAR-resistant B cell tumors
- INT2104-transduced PBMCs killed B cells transduced with CAR20 and GFP similarly
- No evidence of selective advantage towards transduced B cells was seen



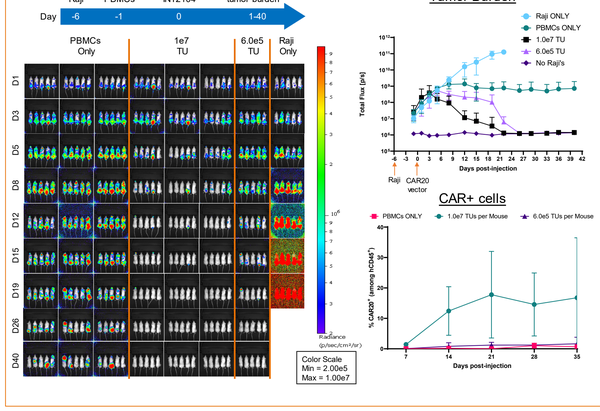
Endogenous B cell depletion after *in vivo* delivery

- Intravenous delivery of INT2104 to CD34$^+$ engrafted NSG mice results in B cell depletion
- CAR$^+$ cells are detectable in peripheral blood starting at Day 7 post-injection and throughout the remainder of the study



Ablation of established B cell tumors

- Established Raji B cell tumors can be controlled following INT2104 administration to NSG MHCI/II KO mice



Looking forward with Interius

- INT2104 exhibits specificity, biological activity, and safety following IV delivery, supporting continued development and transition into the clinic
- Plug and play nature of the Interius bioplatform enables development of new products by changing binder and/or transgene

Acknowledgements

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